REMARKS

A. Status of the Claims

This application was filed as a divisional of co-pending application Serial No. 08/145,826 ('826 application), filed October 29, 1993, which is a continuation-in-part of application Serial No. 07/960,513 filed October 13, 1992. The '826 parent application was originally filed with claims 1-21. In the preliminary amendment accompanying the presently filed divisional application, claims 1-21 were cancelled and claims 43-99 added. In a Preliminary Amendment filed on December 17, 1999, claims 100-118 were added. Because the added claims were numbered erroneously, the Examiner renumbered the pending claims, based on both Preliminary Amendments, to claims 22-97. In the Office Action dated September 8, 2000, claims 22-97 were rejected. These claims are the subject of this response. Appendix A contains a copy of the pending claims in a form Applicants believe is correct.

B. Interview with Examiner Guzo

Applicants' representative met with Examiner Guzo on January 16, 2001 ("interview"), which was sincerely appreciated. The remarks below address the issues discussed at that interview.

C. Claims 22-97 Are Enabled

The Action rejects claims 22-97 under 35 U.S.C. § 112, first paragraph, on grounds that the specification does not enable any person skilled in the art to which it pertains to make and use the invention commensurate in scope with these claims. The Action concedes the specification enables methods for treating cancers comprising administration of the Ad5CMV-

p53 recombinant adenovirus, but it alleges that the specification does not reasonably provide enablement for treating any cancers comprising using any adenovirus comprising the p53 gene. Applicants respectfully traverse this rejection.

a. Applicants Are Surprised by This Rejection

As an initial matter, as discussed in the interview with the Examiner, Applicants note their surprise about this rejection given the issuance of claims in U.S. Patent No. 6,143,290 ('290 patent), which issued on November 7, 2000. Though Applicants realize that different examiners may take different positions, they believe the claims in the instant case are similarly patentable as the claims in the recently issued '290 patent. Claim 1 of that patent reads:

> 1. A method of inducing cell death in human tumor cells comprising administering directly to a tumor comprised of cells which lack functional p53, an adenovirus vector which does not express functional E1B, wherein the vector further comprises and expresses a DNA sequence encoding wild-type p53, and wherein sufficient wild-type p53 is expressed in the tumor cells to induce cell death resulting in regression of the tumor.

In addition, Applicants note that the claims of the '290 patent and the pending claims in the present application are of similar scope than claims reciting adenovirus in other patents recently issued by the PTO, including the present examiner. Many, if not all, of these other issued patents, including those issued by the examiner in the present case, have teachings commensurate with the teaching of the present application yet are not explicitly limited, for example, by adenovirus serotype. Applicants are further surprised by the enablement rejection in this case because of these other issued patents, particularly because the present disclosure teaches *in vivo* treatment methods that are now undergoing advanced clinical trials, evidence of which is lacking from many other issued patents.

b. Specification Enables the Claims

The claims of the present application are directed to methods of "treating a human cancer patient" involving the administration of a composition containing an adenovirus vector comprising a p53 gene. The present specification is enabling for these claims. The disclosure in the specification at pages 39-45 reveals both experimental data and detailed explanations of how to effective target cells *in vivo*. This is more than sufficient to provide objective enablement for the present invention. *In re Marzocchi*, 169 U.S.P.Q. 367 (CCPA 1971) ("The first paragraph of § 112 requires nothing more than objective enablement.").

Example 6 describes an orthotopic lung model for the treatment of lung tumors in mice. In about 75% of control animals (n=20), tumors developed and had a mean volume of 25-30mm^3. In contrast, only 25% of animals treated with p-53 adenovirus (n=8) developed tumors, and those tumors that did form were about 8 mm^3. More importantly, this model specifically addresses the issue of targeting, and the data clearly demonstrate that the treatment was effective at eliminating or reducing tumor development. Thus, targeting issues notwithstanding, the adenovirus-p53 constructs of the present invention are able to enter cells and control tumor growth *in vivo*.

Example 7 goes further in proposing the details for clinical protocols, including routes of administration, dosage of virus particles, devices for administration, post-treatment care, evaluation of clinical efficacy, repeat treatments, monitoring of long term effects and modification of the viral vector. There is nothing in the action that would indicate the deficiency of this disclosure.

Moreover, the Federal Circuit has recently stated, "The enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins Univ. v.*

CellPro, Inc., 152 F.3d 1342, 1361 (Fed. Cir. 1998) (emphasis added) (quoting *Engel Indus. Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991)). This is echoed in the MPEP: "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). As discussed above, the specification does just that.

c. Examiner Has Not Made a *Prima Facie* Case—Cited Articles Are Not Relevant

The Action contends that the "gene therapy art is extremely unpredictable." It elaborates, contending, "Often the ability of a vector to express a therapeutic transgene in cells *in vivo* is dependent upon the specific vector chosen, the vector design, the promoter used to derive expression of the transgene , the method of delivering the vector to the target cells, etc." and cites a number of references. These references, however, do not provide support for this allegation and are not relevant with respect to the *claimed* invention, that is, an adenoviral p53 construct used for treating cancer patients.

Fox, *Nature Biotechnology* 18:143-144, 2000 (Fox), discusses the risks of gene therapy and does not say or suggest that the art of gene therapy is "extremely unpredictable." Furthermore, this article does not address cancer therapy or adenoviral-p53 therapy, which is the subject of the claimed invention.

As for the Kmiec article, *Am.. Scientist* 87:240-247, 1999 (Kmiec), it does not support the position that adenovirus expression of p53 is somehow dependent upon "the specific vector chosen, the vector design, the promoter used. . . , the method of delivering the vector. . . ." It tends to suggest the opposite: under the heading "advantages," Kmiec states that adenovirus

"enters cells efficiently" and "produces high expression of therapeutic gene." More importantly, this article does not address Ad-p53 vectors or their use in cancer treatments. There is no basis in this article that Ad-p53 vectors are unpredictable in their use for the treatment of cancer.

Anderson, *Nature* 392:25-30, 1998, reviews gene therapy and *merely speculates* that "immunogenicity, stability of gene expression, and persistence *in vivo*" may differ with respect to the "exact vector design, the tissue type that the vector is introduced into, and the nature of the transgene insert." This statement does not indicate that the therapy recited by the claims will not be effected, particularly since the transgene insert in this case—p53—is a limitation of the claim. Moreover, this reference does not discuss Ad-p53, the subject matter of the invention. That there is unpredictability in the field of Ad-p53 gene therapy, especially since the specification teaches that Ad-p53 gene therapy works, cannot be gleaned from the Anderson reference.

Similarly, the text of the Verma reference, *Nature* 389:239-242 makes no comment about Ad-p53 cancer therapy that would suggest the claims are not enabled. Applicants emphasize that the claims are directed to Ad-p53 cancer therapy, which the specification teaches, and this reference does not indict the disclosure in any way. For example, the reference does not say that practicing Ad-p53 cancer therapy according to the claims would require undue experimentation. Applicants contend that that the Verma reference is not dispositive on the issue of enablement.

Ross *et al.*, *Human Gene Therapy* 7:1781-1790 (1996) ("Ross"), is focused on human clinical trials involving gene therapy. Applicants' initial comment is that proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). *See also Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994) ("Title 35 does not demand that such human testing occur within the confines of Patent and Trademark (PTO) proceedings."). Furthermore, while

the Ross article makes reference to Ad-p53 therapy, it only says that one of four studies showed marked tumor progression while the other three protocols were not yet fully approved. Thus, it does not address enablement of the claimed invention in any significant way.

Applicants emphasize the claims of the instant applications do not extend to any viral vector containing any transgene for the treatment of any gene. They are directed to an adenoviral vector comprising human p53 for the treatment of cancer, and the specification describes how to make and use the claimed invention. These references do not indicate that the specification is defective in any way.

d. Limitations for Adenovirus Are Not Necessary

With respect to the adenovirus strain, the examiner has not offered any reasoning why, once the general principle of p53 has been established, those of skill in the art could not reproduce the work using other adenovirus strains. The standard of enablement involves a person of ordinary skill in the art, who has knowledge of the art. No evidence has been provided to indicate that that person would not be able to employ the teachings of the application with his knowledge of the art and construct additional p53 adenoviral vectors. For that matter, the examiner has not established that the different strains of adenovirus are so different that common reagents, *e.g.*, supporting cell lines, could not be used for multiple strains. As for "all" essential genes, applicants have disclosed how to use adenovirus vectors that lack certain essential genes. Examples need not be presented for every single embodiment of this aspect of the invention. *In re Borkowski*, 164 U.S.P.Q. 624 (CCPA 1970).

Furthermore, the issue of enablement is whether the specification enables one skilled in the art to practice the claimed invention ***at the time the application is filed.*** *United States Steel*

Corp., 865 F.2d 1247, 1251 (Fed. Cir. 1989). The Federal Circuit has made clear that the mere fact a claim may be found to cover after-developed technology does not in itself lead to a conclusion that the claim is not enabling for the claimed technology. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568 (Fed. Cir. 1990). Thus, the argument that the claims cover second generation adenoviral vectors does not mean the instant claims are not enabled.

e. Another Ad-p53 vector Has Been Employed in Cancer Clinical Trials

Evidence, in the form of papers published after the filing date of this application, can be offered to show that an invention works the way it was described in the specification. MPEP 2164.05. The articles of Wills *et al.*, *Human Gene Therapy* 5:1079-1088 (September 1994) ("Wills") (Appendix B), and Schuler *et al.*, *Human Gene Therapy* 9:2075-2082 (September 1998) ("Schuler") (Appendix C), show that another adenovirus-p53 construct, which is not identical to the construct used in the examples, but is taught by the specification, has been employed in methods of treating cancer. Wills describes an adenovirus 5 vector with either a CMV promoter or Ad2/MLP to drive expression of human p53. The article also purports to show that the Ad-p53 vector inhibited DNA synthesis *in vitro* and reduced tumor growth *in vivo*. The Ad-p53 construct with a CMV promoter was used in a Phase I study on patients with advanced non-small cell lung cancer, as described in the Schuler reference. The study results were "suggestive of a moderate local antiproliferative activity" on tumors.

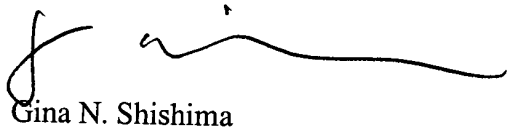
These references offer another example of an adenovirus-p53 vector, both within the scope of the claims and as taught by the specification. They also offer evidence that the claimed invention *operates as disclosed in the specification* and rebut arguments about the unpredictability of the claimed invention.

D. Conclusion

As discussed above, the present specification enables a person of ordinary skill in the art to make and use the claimed invention because 1) the specification shows the adenovirus-p53 employed in the examples of the application is fully operable and effects the treatment method of the claimed invention; 2) other adenovirus-p53 vectors have been employed consistent with the teachings of the disclosure to effect a method of treating cancer; 3) after-developed technology can be encompassed by a fully enabled claim; 4) a burden of enablement has not been met because the cited references do specifically address the claimed invention; and 5) nonetheless, even if such a case had been made, evidence of other operable vectors shows claimed invention is enabled.

The Examiner is invited to contact the undersigned attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



Gina N. Shishima
Reg. No. 45,104
Attorney for Applicant

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3081

Date: March 8, 2001